REMARKS

Amendments to the Claims

Claims 1-5, 8-10, 21-25, 27-30, 60, 70, 89, 91 and 92 were pending.

Claim 60 has been amended to delete the phrase "b) removing at least a portion of the intervertebral disc to create a disc space, and c) inserting a spinal implant into the disc space."

No new matter has been added. Entry of the amendment is requested.

Rejection of Claims 1-3, 5, 8-10, 21-23, 25, 27-30, 70, 89, 91 and 92 Under 35 U.S.C. § 103(a)

Claims 1-3, 5, 8-10, 21-23, 25, 27-30, 70, 89, 91 and 92 have been rejected under 35 U.S.C. § 103(a) for being unpatentable over Cullis-Hill (U.S. Patent No. 6,593,310; hereinafter, "Cullis-Hill") in view of Tobinick (U.S. Publication No. 2001/0026801; hereinafter, "Tobinick") and further in view of Radomsky (U.S. Patent No. 5,942,499; hereinafter, "Radomsky").

Cullis-Hill teaches a method of treating osteoporosis with polysulfated polysaccharides, (col. 3, lines 55-58). In some embodiments, it lists compositions comprising other agents such as "Fosamax, estrogen, calcium supplements, vitamin D supplements, calcitriol, calcitonin, testosterone, anabolic steroids and SERM (selective estrogen receptor modulator)" (col. 3, lines 27-37). Although Cullis-Hill notes that estrogen is an example of an anti-resorptive agent (col. 1, lines 59-61), it also teaches that: "estrogen failed to restore bone back to young adult levels in the established osteoporotic skeleton" (col. 1, lines 64-66). Cullis-Hill teaches that:

> Moreover, long-term estrogen therapy has been implicated in a variety of disorders, including an increase in the risk of uterine cancer, endometrial cancer and possibly breast cancer, causing many women to avoid this treatment. The significant undesirable effects associated with estrogen replacement therapy support the need to develop alternative therapies for osteoporosis that have the desirable effect on serum LDL but do not cause undesirable effects. (col. 1, line 66 through col. 2, line 7)

Cullis-Hill does not teach or suggest an anti-resorptive agent that is a highly specific cytokine antagonist comprising a monoclonal antibody that inhibits TNF-α as in present Claims 1, 21, 70 and 89, because the compounds described in Cullis-Hill, as well as those enumerated above, include neither an antibody nor any other highly specific TNF-α inhibitor.

The teachings of Tobinick are directed to methods for inhibiting the action of pro-inflammatory cytokines by using a monoclonal antibody that specifically inhibits TNF-α (*e.g.*, etanercept or infliximab) in order to treat nerve or muscle injury. Tobinick states that:

> The present invention relates to specific cytokine antagonists which are provided for the treatment and prevention of damage to the optic nerve, other cranial nerves, brain, spinal cord, nerve roots, peripheral nerves or muscles caused by any one of the following: a herniated nucleus pulposus, osteoarthritis, other forms of arthritis, disorders of bone, disease, or trauma. (Tobinick, Abstract; emphasis added).

Tobinick also teaches that:

> **[0038]** Trauma, injury, compression and disease can affect individual nerves, nerve roots, the spinal cord, or localized areas of muscle. The disorders which are of most concern and which are included here are the following:
> **[0039]** Spinal Cord Injury
> **[0040]** Spinal Cord Compression
> **[0041]** Herniated Interverterbral [*sic*] Disc (herniated nucleus pulposus)
> **[0042]** Glaucoma
> **[0043]** Bell's Palsy
> **[0044]** Localized Muscular Disorders, including acute muscle pulls, muscle sprains, muscle tears, and muscle spasm.
> **[0045]** Alzheimer's Disease
> **[0046]** Postherpetic Neuralgia (Tobinick at page 3 right column, paragraphs 38 through 46; emphasis added)

As shown above, the teachings of Tobinick are directed to the treatment of one or more damaged nerve or muscle tissues, not uncoupled resorbing bones. Tobinick does not teach or suggest that an antibody against TNF-α is effective for treating uncoupled resorbing bones.

Radomsky teaches compositions for promoting bone growth. Radomsky's compositions include hyaluronic acid (HA) and a growth factor such as fibroblast growth factor (FGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), insulin-like growth factors (IGF), and transforming growth factors (TGF) including BMP 1-12 and GDF (col. 1, lines 19 and 34-39). These compositions can be administered at the site of desired bone growth including vertebral compression fractures and in pathological bond defects associated with

osteoporosis (col. 2, lines 50-58). Radomsky does not teach or suggest that a monoclonal anti-TNF-α antibody is effective for treating uncoupled resorbing bones. In fact, Radomsky does not disclose any aspect of a cytokine antagonist, particularly an anti-TNF-α antibody, for promoting bone growth.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in some knowledge generally available in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success to arrive at claimed subject matter. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art and not based in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), M.P.E.P. § 706.02(j) (revision August 2006).

No Reasonable Expectation of Success

First, a person of ordinary skill in the art would not have been motivated to combine the teachings of these references with a reasonable expectation of success because none of the cited references, neither Cullis-Hill, Tobinick nor Radomsky, teaches or suggests that a highly specific anti-TNF-α agent is useful for treating uncoupled resorbing bones. The Office Action states that:

> The person of ordinary skill would have reasonably expected success because the combinatorial compositions comprising cytokine antagonists and other active agents which help in treating osteoporosis were well known in the art at the time of the instant invention, as evidenced by the 'Cullis [*sic*] patent and one of skill in the art would have expected success by substituting the species of infliximab as taught by the '801 patent with the anti-TNF agents taught by the Cullis patent (the Office Action at page 5).

Applicants respectfully disagree with the Examiner's interpretation of Cullis-Hill and Tobinick (the '801 patent). As noted above, the anti-resorptive agents taught by Cullis-Hill are compounds such as polysulfated polysaccharides, polysulfated dextran, polysulfated cyclodextran, polysulfated chondroitin, and pentosan polysulfate provided in conjunction with a number of compounds including estrogen. None of the compounds disclosed in Cullis-Hill are

monoclonal antibodies as in the present invention or any other biologic. Nor is there any teaching or suggestion in Cullis-Hill that the disclosed compounds can inhibit TNF-α or that such inhibition would lead to treatment of uncoupled resorbing bones. Notably, Cullis-Hill provides no data regarding administration of estrogen. It only provides data regarding administration of polysulfated polysaccharides. Tobinick does not teach or suggest that a monoclonal anti-TNF-α antibody would be effective for treating uncoupled resorbing bones. Tobinick only teaches that such an antibody may be useful for treating damaged nerve or muscle tissue(s). Radomsky, which only teaches about the use of HA and growth factors, does not compensate for the deficiency. Radomsky does not disclose any aspect of a cytokine antagonist, particularly an anti-TNF-α antibody, for promoting bone growth. As such, none of the cited references, alone or in combination, teaches or suggests that a highly specific anti-TNF-α agent is useful for treating uncoupled resorbing bones, and there is no motivation or suggestion to modify or combine the references to do so Without having this knowledge or a proper guidance, one of ordinary skill in the art would not have had a reasonable expectation of success in arriving at the present invention directed to methods of treating an uncoupled resorbing bone with a monoclonal antibody that inhibits TNF-α.

No Motivation to Combine the Teachings of Cullis-Hill with the Teachings of Tobinick and Radomsky

Second, absent impermissible hindsight, one of ordinary skill in the art would not have been motivated to combine the teachings of Cullis-Hill with the teachings of Tobinick and Radomsky to arrive at the present invention. The Office Action states that:

> "The person of ordinary skill in the art could have combined the elements as claimed by known methods to produce a composition comprising infliximab and bone forming agents. One of skill in the art would have recognized that the results of the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time the invention was made, as demonstrated by the teachings of the Cullis patent and 801 publication" (the Office Action at page 5).

Applicants disagree. As discussed above, neither Cullis-Hill, Tobinick nor Radomsky, individually or in combination, teaches or suggests that a monoclonal antibody against TNF-α

can be effective for treating uncoupled resorbing bones. Moreover, none of the references indicates that estrogen can be an anti-TNF-α agent. In fact, estrogen is not a monoclonal antibody against anti-TNF-α. Without the proper teaching or guidance, prior to applicants' application teachings, the result as to whether a monoclonal antibody against anti-TNF-α is effective for treating resorbing bone would have been highly unpredictable to one of ordinary skill in the art. Because of this unpredictability, one of ordinary skill in the art would not have been motivated to combine the teachings of Cullis-Hill with the teachings of Tobinick and Radomsky to arrive at the present invention.

Claim 89

The references of the record, individually or in combination, do not teach all elements of Claim 89, for the reasons stated above and for the following additional reasons. Independent Claim 89 states as follows:

> A method of therapeutically treating an uncoupled resorbing bone in a patient, comprising the steps of:
> a) administering an effective amount of a first formulation comprising a bone forming agent into the bone, and
> b) administering an effective amount of a second formulation comprising an anti-resorptive agent into the bone, wherein the anti-resorptive agent is a highly specific cytokine antagonist comprising a monoclonal antibody that inhibits TNF-α, *wherein the second formulation is in the bone in an effective amount for at least one month.*
> (emphasis added)

As shown above, present Claim 89 is directed to administration of an anti-resorptive agent comprising a monoclonal antibody that inhibits TNF-α into the bone and the agent remains in the bone in an effective amount for at least one month. None of the references of record teaches or suggests that the anti-resorptive agent (*i.e.*, a monoclonal antibody that inhibits TNF-α) remains in the bone for at least one month. Because the prior art references, when combined, do not teach or suggest all elements of Claim 89, a *prima facie* case of obviousness has not been established with regard to Claim 89.

In summary, the claimed invention would not have been obvious to one of ordinary skill in the art because a *prima facie* case of obviousness has not been established. Not all elements of the claims are taught or suggested by the combined teachings of the prior art references. One of ordinary skill in the art would not have been motivated to combine the teachings of the references of record to arrive at the claimed invention. Finally, there was no reasonable expectation of success in arriving at the present invention.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 4 and 24 Under 35 U.S.C. § 103(a)

Claims 4 and 24 have been rejected under 35 U.S.C. § 103(a) for being unpatentable over Cullis-Hill (U.S. Patent No. 6,593,310) in view of Tobinick (U.S. Publication No. 2001/0026801) and further in view of Radomsky (U.S. Patent No. 5,942,499) and further in view of Boyle *et al.* (U.S. Patent Publication 2003/0207827; hereinafter, "Boyle"). These claims are directed to methods of the claimed invention wherein the patient is post-menopausal.

The Office Action states that: "It would have been obvious to one of ordinary skill in the art at the time of instant invention to utilize the bone forming agent and infliximab to post menopausal women as a patient motivated by the teachings of Boyle et al. teaching the administration of antiresoptive [*sic*] agents for treatment of osteoporosis in post menopausal women" (the Office Action, bridging paragraph between page 6 and page 7).

The teachings of Cullis-Hill, Tobinick and Radomsky are discussed above.

Boyle teaches that there exists a direct relationship "between osteoporosis and the incidence of hip, femoral, neck and inter-trochanteric fracture in women 45 years and older" (Boyle at page 9, paragraph [0095]). Boyle also teaches that osteoprotegrin (OPG) acts as a receptor of the TNF family and may prevent a receptor-ligand interaction (Boyle at page 4, paragraph [0043]).

Boyle, however, does not teach or suggest an antibody which inhibits TNF-α as in the presently claimed invention. OPG is not an antibody, it is a receptor, and Boyle does not teach that it binds or inhibits TNF-α. In fact, in its three-dimensional structure modeling, Boyle demonstrates a co-crystallization of OPG protein complexed with TNF-β in order to illustrate the

interaction of OPG with its ligand (*see* Boyle, Figure 11; and paragraphs [0019] and [0148]). Although Boyle's teaching in Figure 11 may suggest that OPG could bind to TNF-β, Boyle makes no reference as to whether the effect of OPG on the bone density is via TNF-α. It is known that the impacts of TNF-α and TNF-β on the inflammatory response pathway are not the identical.[1] Further, Saidenberg-Kermanac'h *et al.*[2], a post-filing publication (published in November, 2004) the abstract of which is submitted herewith as Exhibit A, demonstrate that the molecular mechanisms by which OPG and anti-TNF-α antibodies affect the physiology in osteoporotic bones are distinct from each other. Specifically, Saidenberg-Kermanac'h *et al.* state as follows:

> INTRODUCTION: Rheumatoid arthritis (RA) is associated with focal and systemic bone loss involving cytokines such as RANKL and TNF-alpha. RANK-L promotes focal and systemic osteoporosis, whereas osteoprotegerin (OPG) inhibits bone resorption. Although anti-TNF-alpha antibodies (anti-TNF-alpha Ab) decrease joint inflammation and bone erosions, their effects on bone loss are unknown...RESULTS: Anti-TNF-alpha Ab, but not OPG, decreased the clinical arthritis score ($P<0.02$ vs. saline) and the histological score of inflammation... Compared with saline, OPG increased trabecular bone volume (BV/TV) ($P<0.02$), decreased trabecular separation ($P<0.02$), and decreased the bone formation rate (BFR) ($P<0.01$). Anti-TNF-alpha Ab produced no significant changes in bone volume or trabecular separation but increased trabecular thickness ($P<0.02$ vs. saline) to a value close to that in naive mice, suggesting preservation of bone formation. No additive effects of OPG and anti-TNF-alpha Ab were found. CONCLUSIONS: Systemic OPG and anti-TNF-alpha Ab therapy prevented bone loss in CIA mice through distinct mechanisms involving decreased bone resorption and preserved bone formation....

This statement by Saidenberg-Kermanac'h *et al.* directed to the distinct role of the anti-TNF-α antibodies on osteoporotic bones establishes that it was not obvious for one of ordinary skill in

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[1] TNF-β is mainly produced by T cells and recognized by the lymphotoxin beta (LT-β) receptor in a complex with LT-β. TNF-α is produced by macrophages and recognized by tumor necrosis factor receptors I and II (TNFRI and II). TNF-α is expressed on the cell membrane and then hydrolyzed to release as a soluble form, which forms homotrimers. TNF-β has no cell membrane attachment domain but can form either membrane-anchored heterotrimers with LT-β or soluble homotrimers. See for example, Exhibit B1 and B2 submitted herewith, slides downloaded from website. http://www.sigmaaldrich.com/life-science/cell-biology/learning-center/pathway-slides-an on 10/20/09.

[2] Saidenberg-Kermanac'h *et al.* "TNF-alpha antibodies and osteoprotegerin decrease systemic bone loss associated with inflammation through distinct mechanisms in collagen-induced arthritis." *Bone*, 35:1200-1207 (2004).

the art to combine the teachings of Boyle with the teachings of the references of record to arrive at the claimed invention.

Since Boyle does not compensate for the deficiency in teachings of Cullis-Hill, Tobinick and Radomsky for independent Claims 1 and 21, Claims 4 and 24, which are dependent on Claims 1 and 21, respectively, are not rendered obvious over these references of record. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 60 Under 35 U.S.C. § 103(a)

Claim 60 has been rejected under 35 U.S.C. § 103(a) for being unpatentable over Cullis-Hill (U.S. Patent No.: 6,593,310) in view of Tobinick (U.S. Publication No.: 2001/0026801) and further in view of Trieu *et al.* (U.S. Patent Publication 2002/0026244; hereinafter, "Trieu").

The Office Action states that: "It would have been obvious to the one of ordinary skilled [*sic*] in the art at the time the invention was made to incorporate highly specific cytokine antagonist such as infliximab as taught by '801 to the teaching of Trieu since the reference teaches advantage of the same in treating osteoporosis with [pharmacological agents] such as bone morphogenetic protein etc (the Office Action, bridging paragraph between page 7 and page 8).

As noted above, Claim 60 has been amended to delete the phrase "removing at least a portion of the intervertebral disc to create a disc space, and inserting a spinal implant into the disc space" to better clarify the claimed invention.

The teachings of Cullis-Hill and Tobinick are discussed above.

Trieu's teachings are directed to removal of the natural nucleus pulposus of the intervertebral disc and placement of a nucleus pulposus implant in the intervertebral disc, not into the bone. Although Trieu teaches that nucleus pulposus implants can deliver growth factors which would repair annulus fibrosis and the endplates of the disc (*see* Trieu, paragraph [0101] and [0102]), it does not teach or suggest any placement of its implants into the bone.

Lack of Prima Facie Case of Obviousness

The references of record in combination do not teach or suggest all elements of Claim 60. The teachings of Trieu are limited to a method of administering a formulation from an implant

placed in the nucleus pulposus in between two vertebral bones. The Office Action characterizes this type of administration as "local administration in between bones" (the Office Action at page 7; emphasis added). Administration by releasing a formulation from an implant placed in between two intact bones (*i.e.*, two vertebrae) is not equivalent to, nor does it suggest, administration which involves delivering the formulation into the bone as in present Claim 60. In Claim 60, the device which releases the bone forming agent and anti-resorptive agent is inserted into the vertebral body (*i.e.*, "backbone"). Neither Cullis-Hill, Tobinick nor Trieu teaches or suggests placing a device in the vertebral body. Moreover, Trieu is focused on a condition other than osteoporosis. One would not have been motivated to modify its teachings to treat an osteoporotic patient by inserting an implant into the bone. Therefore, the references of record do not teach all elements of Claim 60.

Further, none of these references teaches or suggests that a monoclonal antibody against TNF-α is useful for treating osteoporotic bones as discussed above. Without having this knowledge, one would neither have been motivated to combine the teachings of these references, nor have had a reasonable expectation of success to arrive at the present invention. Therefore, a *prima facie* case of obviousness has not been established.

Superiority of the Present Invention Over the Prior Art

The prevent invention achieves an advantage over the teachings of Trieu by delivering the formulation directly into the vertebral bone. Osteoporosis involves the progressive resorption of bone which requires long-term treatment throughout the resorptive process. The present Specification specifically teaches the desirability of long term administration in treating osteoporosis[3] and the direct advantages of administering the formulation into the bone in such treatment. The Specification provides that: "[S]ince the cortical shell of the bone comprises a relatively dense structure, this outer component of the bone may prevent the out-diffusion of the drug and so may provide a suitable depot for the osteotherapeutic drug, thereby increasing its

[3] "Because the osteoporosis ("OP") involves the progressive resorption of bone in which many factors are involved, in many instances, simply providing a single dose or even a regimen over the space of a few days may not be sufficient to manage the OP...Accordingly, it is desirable for the AR and/or BF agent to remain within the bone as long as possible in a pharmaceutically effective amount" (the Specification at page 39, line 26 through page 40, line 1).

half-life in the target bone" (the Specification at page 7, lines 14-17). The Specification teaches the difference in expected half-life of REMICADE® infliximab when this agent is administered systemically versus directly into the bone (about 1 week *vs.* about 9 weeks).[4] Trieu does not contemplate this advantage because Trieu's disclosed method is limited only to administering the formulation from an implant placed in the disc, not the vertebral body. Further, in addition to the improvement of the potency and half-life of the formulation, the present invention also provides a reduction in chances of unwanted side effects associated with long-term therapy involved in treatment of osteoporosis by keeping the formulation from diffusing outside of the target vertebral bone.[5]

Finally, neither Trieu nor any other references of record teaches or suggests the desirability for long-term treatment in cases of osteoporosis. As noted above, the teachings of Trieu are directed to repairing physical damage to the intervertebral disc (*see* Trieu page 9, paragraphs [0101] and [0102]). Such physical damage may include a surgical incision made to the annulus fibrosis during the nucleus pulposus implantation procedure, which can be repaired with a rather short-term treatment that promotes the healing process. In contrast, bone damage caused by osteoporosis as described in the Specification may require at least 1 month to 6 or 12 months or an even longer time to reverse the resorptive process and restore the bone forming activity (*see* the Specification at page 16, lines 15-23 and pages 39 through 40, bridging paragraph). Thus, the placement of the device adapted to deliver an effective amount of a bone forming agent and an anti-resorptive agent into the vertebral body itself achieves a significant advantage over the teachings of Trieu.

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[4] "For example, suppose a clinician administered 0.3 ml of 60 mg/ml REMICADE® infliximab into a 2.7 cc bone, thereby producing an infliximab concentration in the bone of about 6 mg/ml, or 6 parts per thousand. Without wishing to be tied to a theory, if infliximab has the same half-life within a bone as it does when administered systemically (*i.e.*, about 1 week), then the concentration of infliximab would remain above about 10 ppm for about 9 weeks. Therefore, if another dose were needed, the clinician would only need to provide the second dose after about two months" (the Specification at page 45, lines 16-29).

[5] "For example, if it is believed that a BF and/or AR agent is effective when present in the range of about 1-10 mg/kg or 1-10 ppm (as is believed to be the case for the TNF antagonist REMICADE® infliximab as an AR agent), and since the cancellous portion of a cervical vertebral body has a volume of about 3 ml (or 3 cc or 3g), then only about 3-30 μg of the HSCA would need be administered to the bone in order to provide a long lasting effective amount of the drug. The small amounts available by this route reduce the chances of deleterious side effects of the BF and/or AR agent" (the Specification at page 45, lines 15-21; emphasis added).

Accordingly, the present invention provides a significant advantage over the teachings of the prior art references which was not recognized by one of ordinary skill in the art at the time of the invention.

Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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